

### **Remarks**

In view of the foregoing amendments and the following remarks, Applicant respectfully requests reconsideration of the pending claims. Claims 21 through 39 and 44 are pending in this application, and are the subject of the present examination. Claims 45 through 58 have been added. The Examiner withdrew the previous objection to claims 21-23, 26-32 and 39, the previous rejection of claims 24-25 and 32-35, under 35 USC § 101, and the previous rejection of claims 21-23, 26, 29 and 36-38 under 35 USC § 112, second paragraph. Claims 24, 27, 30, 34 and 39 are allowed.

Applicants note that there appears to be an error in the numbering of the claims, as discussed in a telephone conversation with the Examiner on May 29, 2003. The Examiner is respectfully requested to review the claims and renumber them as appropriate.

Newly added claims 45 through 53 recite nucleic acids encoding fragments, expression vectors comprising such nucleic acids, host cells comprising such expression vectors, methods of preparing polypeptides and the polypeptides themselves. Applicants respectfully submit that the discussion herein regarding fragments is pertinent to the newly added claims. Support for these claims is found in the specification, page 18 line 4, through page 19, line 7. Accordingly, Applicants respectfully submit that these claims are allowable.

Newly added claims 54 through 58 recite variants of the polypeptide of SEQ ID NO:8 that are at least 80% identical to SEQ ID NO:8 and that maintain activity in IKB $\alpha$  or p38 MAP kinase phosphorylation or in cell surface expression of ICAM-1, and nucleic acids encoding such variants, expression vectors comprising such nucleic acids, host cells comprising such expression vectors, and methods of preparing the claimed variant polypeptides. Support for these claims is found in the specification, page 15 line 10, through page 18, line 2.

Applicants respectfully submit that the discussion herein regarding fragments is pertinent to newly added claims 54 through 58, and that one of ordinary skill in the art could prepare such variants and test them for activity. Characterization of IL-1 epsilon polypeptides can be carried out utilizing methods that were known in the art at the time the present application was filed, and preparing variants thereof and testing them for activity is a matter of routine experimentation. Accordingly, Applicants submit that these claims are allowable.

### **Rejections under 35 U.S.C. § 112**

Claims 21 through 23, 26, 29, and 36 through 38 remain rejected under 35 USC § 112, first paragraph, because the specification, while being enabling for specific nucleic acid molecules and polypeptides, allegedly does not enable fragments of the latter that are active in IKB $\alpha$  or p38 MAP kinase phosphorylation or in cell surface expression of ICAM-1. The Examiner asserts that practice of the instant invention would require additional characterization in order to obtain

functional and structural data needed to permit one to produce a fragment that meets both structural and functional requirements of the instant claims, and further that such characterization studies constitute undue experimentation. Applicant respectfully disagrees.

Applicant reiterates that in the art of molecular biology the level of ordinary skill is very high and knowledge of a variety of sophisticated techniques and methods is presumed, as discussed in Response and Amendment A, which is incorporated by reference herein. Moreover, the PTO has made it clear that the teaching required to support claims encompassing a number of molecules which are further limited by reciting an operable activity, is satisfied if the disclosure teaches how to make a candidate molecule and how to test the candidate molecule for the activity. *Ex parte Mark* 12 USPQ2d 1904 (Bd. Pat. App. & Int'f 1989). Since the specification, in combination with the knowledge of those skilled in the art, teaches how to make IL-1 epsilon fragments and the specification teaches how to test for activity in IKB $\alpha$  or p38 MAP kinase phosphorylation or in cell surface expression of ICAM-1, the specification enables the subject claims. Any requirement that Applicant limit the claims to specific fragments does not adequately protect Applicant in view of the scope of the invention and the disclosure. Thus, to demand that Applicant limit the claimed invention to specific IL-1 epsilon fragments when it is well within the knowledge of those skilled in the art to use routine experimental techniques to make and test IL-1 epsilon DNA and polypeptide fragments that are active in IKB $\alpha$  or p38 MAP kinase phosphorylation or in cell surface expression of ICAM-1 is improper.

Moreover, Applicant respectfully submits that any characterization that might be necessary is within the purview of one of ordinary skill in the art. As evidence of this, Applicant submits herewith as Exhibit 1 an article by Smith et al. (*J. Biol. Chem.* 275(2):1169; 2000), describing four new members of the IL-1 superfamily. On page 1170, under the subheading *Structure Modeling*, Smith et al. discuss the structure modeling of the IL-1 superfamily utilizing a sequence alignment based on that known in the art for the IL-1's and IL-18, and implementing several programs that were also known in the art to further analyze and compare the structural aspects of IL-1 superfamily members (see Exhibit 2 for publication dates and abstracts for these references; copies will be provided at the Examiner's request). Thus, as shown in Figure 1, the sequence alignment of IL-1 epsilon (referred to in Smith et al. as FIL-1 $\epsilon$  or FIL-1 $\epsilon$ ) with other IL-1 superfamily members allows one of ordinary skill in the art to predict the beta strands of the presently claimed IL-1 family member. Moreover, as shown in Figure 3, the amino acid sequence of IL-1 epsilon can be folded into a structure that superimposes well onto the crystal structure of IL-1 alpha and IL-1 beta, with minimal energy violations.

Additionally, there have been several studies mapping receptor-binding sites of IL-1 family members by site-directed mutagenesis, as discussed in Evans et al. (*J. Biol. Chem.* 270(19):11477; 1995, enclosed herewith as Exhibit 3). Those of ordinary skill in the art could, by the application of routine experimentation, carry out similar studies, and verify the receptor

binding sites for IL-1 epsilon. Moreover, the crystal structure of IL-1 receptor complexed with IL-1 beta has been deduced (Vigers et al., *Nature* 386:190; 1997, Exhibit 4), as has the crystal structure of IL-1 receptor complexed with IL-1ra (Schreuder et al., *Nature* 386:194; 1997, Exhibit 5). Such studies, performed using methods that are known in the art, can be similarly applied to IL-1 epsilon, allowing one of ordinary skill in the art to prepare a genus of IL-1 epsilon polypeptides, including fragments of the polypeptides of SEQ ID NO:8 and 13 (as well as polypeptides that are 80% identical to that of SEQ ID NO:8) that are active in IKB $\alpha$  or p38 MAP kinase phosphorylation or in cell surface expression of ICAM-1.

Accordingly, one of ordinary skill in the art could, at the time the instant application was filed, use the disclosed sequence information together with techniques that were known in the art, to predict a structure for IL-1 epsilon. Moreover, one of ordinary skill in the art could, at the time the application was filed, use the crystal structure of IL-1 complexed with receptor or antagonist to predict which residues are important for receptor binding. Furthermore, one of ordinary skill in the art could, at the time the application was filed, use the known mutational analysis of IL-1 to predict residues important for activity of IL-1 epsilon. Applicant respectfully submits that this characterization would allow one of ordinary skill in the art to predict fragments of IL-1 epsilon that would be likely to retain activity. To prepare and test these fragments would be a matter of routine experimentation. Applicants request that the rejection be withdrawn.

Claims 21, 23, 25, 26, 28, 29, 31-33, 35-38 and 44 were rejected under 35 USC § 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising a polynucleotide that encodes the polypeptide set forth in SEQ ID NO:8, allegedly does not provide enablement for an isolated nucleic acid comprising a polynucleotide that encodes the polypeptide set forth in SEQ ID NO:6 13 or fragments thereof. Applicant respectfully disagrees; nonetheless, in an effort to be cooperative and speed allowance of the claims, Applicants are submitting herewith a Declaration of John Sims, to provide objective evidence that the polypeptide of SEQ ID NO:13 (having an Arg at residue 12) is biologically active. Accordingly, Applicants request that the rejection as it relates to Arg12 IL-1 epsilon be withdrawn.

Moreover, Applicants respectfully point out that claim 33 is directed to the polypeptide of SEQ ID NO:6, irrespective of the ability of such polypeptide to activate IKB $\alpha$  or p38 MAP kinase phosphorylation or induce cell surface expression of ICAM-1. The polypeptide of claim 33 will have utility as a research tool in further clarifying the activity(ies) of IL-1 epsilon, as an immunogen in generating antibodies, and as a reagent in differentiating antibodies that bind to the region common to SEQ ID NOs:6, 8 and 13. Accordingly, Applicants request that the rejection as it relates to the polypeptide of SEQ ID NO:6 be withdrawn.

**CONCLUSIONS**

Claims 21 through 39 and 44 through 58 are now pending in the application and are believed to be in condition for allowance. If the examiner has any questions or concerns about the present claims, she is asked to contact the undersigned at the direct dial number given below, to facilitate prosecution and speed allowance of the claims.

Respectfully submitted,



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